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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Region III - 8th & Walnut Sts.

Philadelphia, Pa. 19106

SUBJECT: Toxicologic Assessment of Fyrol PCF  
NEW CASTLE COUNTY SPILL SITE (WITCO)

DATE: 3 Oct 84

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Introduction

Fyrol PCF is a type of "Tris" fire retardant which has heavily contaminated groundwater in New Castle County, Delaware. Thousands of well water samples confirm presence of Fyrol PCF often in excess of 100 ppm. The structural relationship of Fyrol PCF to mutagenic Fyrol FR2 and mutagenic and carcinogenic Tris BP, as well as to the chloropropyl ethers, has raised considerable concern for human health due to groundwater contamination in New Castle County. EPA has recently summarized exhaustive testing of Fyrol PCF and in this memorandum I will evaluate mutagenic, carcinogenic and toxicity data with regard to assessing human health risk from the New Castle County spill.

Tris Compounds

"Tris" refers to three ethyl or propyl molecules, normally substituted with chlorines or bromines, which are attached to a central phosphate molecule. Structural formulae for the following "Tris" fire retardants are shown on the next page:

Fyrol PCF tris ( $\beta$ -chloroisopropyl) phosphate

Fyrol CEF tris ( $\beta$ -chloroethyl) phosphate

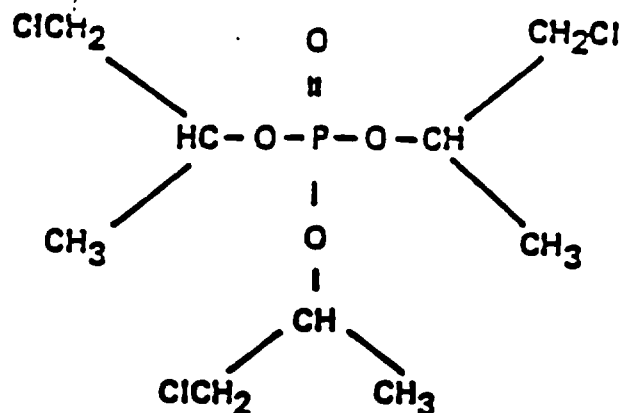
Fyrol FR2 tris (1,3-dichloroisopropyl) phosphate

Tris BP tris (2,3-dibromopropyl) phosphate

Data on Toxicology of Other Tris Compounds

Fyrol FR2 was the first compound tested for mutagenicity, which tests were positive resulting in its ban from children's sleepwear. Tris BP has ten times the mutagenic potency of Fyrol FR2 and in addition is an animal carcinogen. This report concerns Fyrol PCF

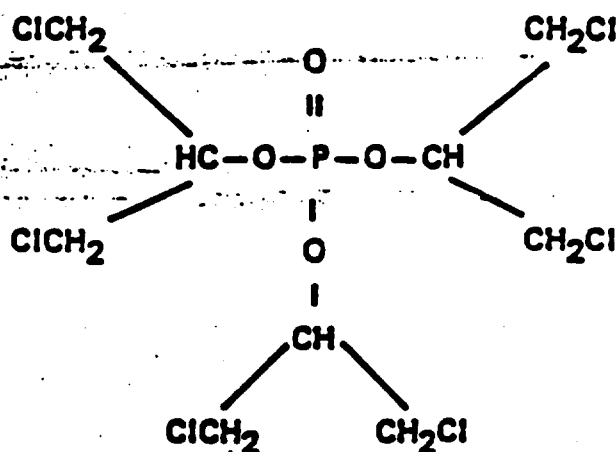
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**Fyrol PCF**

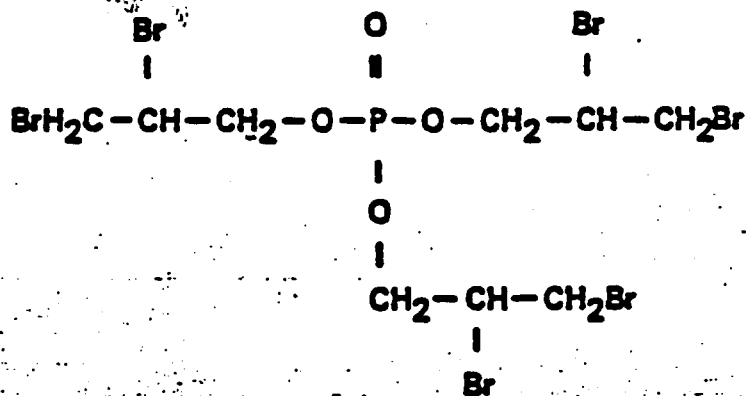
[Tris( $\beta$ -chloroisopropyl)phosphate]

$\leftarrow$  if ( $\beta$ -chloroethyl) = **Fyrol CEF**



**Fyrol FR2**

[Tris(1,3-dichloroisopropyl)phosphate]



Tris(2,3-dibromopropyl) phosphate = **BP**

**Figure 1. Structures for Fyrol PCF, Fyrol FR2, and Tris(2,3-dibromopropyl)phosphate.**

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which appears not to be mutagenic in a wide number of test systems. Tests regarding Fyrol CEF are still in progress.

#### Mutagenicity of Fyrol PCF

Despite the fact that Fyrol PCF is similar structurally to a number of mutagens, the compound itself is not mutagenic when tested in eleven independent test systems. Five of these tests were subcontracted to independent investigators by EPA, five were subcontracted to Litton Bionetics, Inc., by Stauffer Chemical Co. and one test appeared independently in the literature.

The battery of mutagenic tests on Fyrol PCF includes divergent cell systems:

- 1) Ames test, using Salmonella bacteria
- 2) Chinese hamster ovary (CHO) cells
- 3) Primary rat hepatocyte cultured cells
- 4) Diploid human fibroblasts (WI38)
- 5) Mitotic gene conversion in Saccharomyces yeast
- 6) Mouse lymphoma cells

Also several in vivo tests were conducted on whole animals, including:

- 7) Sex-linked recessive lethal mutation induction in Drosophila
- 8) Sister chromatid exchanges in rat bone marrow

And finally teratogenesis of Fyrol PCF was tested in a frog embryo system.

The results of all these studies, some duplicated in independent laboratories, are shown on the next page. The important column is the first in which mutagenesis is scored as either negative (-) or possibly weak (wk?). I have examined the data of the November 1983 EPA report and am satisfied that these summaries are accurate. We also have on file each of the Litton Bionetics tests done for Stauffer Chemical in 1978.

It is important to note that in addition to the wide range of test systems employed, many of them utilizing human or other mammalian cells, that Fyrol FR2 and/or Tris BP were almost always included in the tests as positive controls. The only deviation from published results in these tests came from the inability to show Tris BP mutagenicity in Drosophila among these positive controls (see p. 5).

TABLE 1. SUMMARY OF MUTAGENICITY TEST RESULTS FOR FYROL PCF

<u>Tests Sponsored by EPA*</u>	<u>Results†</u>	<u>Reference</u>	<u>Principal Investigator</u>
Ames <u>Salmonella</u> /microsome assay - preincubation test protocol	-	Case et al. (1983)	K. Mortelmans, SRI International
Chinese hamster ovary/HGPRT assay	wk?§	Schenley et al. (1983)	A. Hsie, Oak Ridge National Laboratory
Hepatocyte primary culture DNA repair test	-	Tong and Williams (1983)	G. Williams, Naylor Dana Institute
<u>Drosophila</u> sex-linked recessive lethal test	-	Nix et al. (1983)	C. Nix, Oak Ridge National Laboratory
Sister chromatid exchanges <u>in vivo</u> and <u>in vitro</u>	-	Tice (1983)	R. Tice, Brookhaven National Laboratory
<u>Tests Sponsored by Stauffer Chemical Corporation</u>			
Ames <u>Salmonella</u> /microsome assay - plate test protocol	-	Litton Bionetics, Inc. (June 1976, May 1978)	
Yeast mitotic gene conversion assay	-7§	Litton Bionetics, Inc. (June 1976, May 1978)	
Mouse lymphoma TK+/- assay	wk?§	Litton Bionetics, Inc. (February 1978)	
Unscheduled DNA synthesis in WI-38 cells	wk?	Litton Bionetics, Inc. (September 1978)	
Rat bone marrow assay	-§	Litton Bionetics, Inc. (October 1978)	
<u>Published Literature</u>			
Ames <u>Salmonella</u> /microsome assay - plate test protocol	-	Nakamura et al. (1979)	

\*Tests were selected, protocols were developed, and contracts were monitored by the Reproductive Effects Assessment Group.

†(-) designates a negative result, (wk?) designates a questionable weak or marginal result that was not dose-related and/or not repeatable, (-?) designates a questionable negative.

§The authors concluded that Fyrol PCF does not appear to be mutagenic.

¶Increased response in isolated data set.

Source: Mutagenicity Assessment of Fyrol PCF  
EPA Office of Health and Environmental Assessment  
November 1983 (OHEA-R-114)

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TABLE 3. COMPARISON OF MUTAGENICITY TEST RESULTS FOR FYROL PCF WITH RESULTS FOR THE STRUCTURALLY RELATED COMPOUNDS FYROL FR2 AND TRIS(2,3-DIBROMOPROPYL)PHOSPHATE (TRIS-BP)

Gene Mutation Tests:	Results*			Reference†
	Fyrol PCF	Fyrol FR2	Tris-BP	
Ames <u>Salmonella</u> /microsome assay - preincubation test	-	wk	+	Case et al. 1983
plate test	-	wk	§	Litton Bionetics Inc., June 1976, May 1978 Brusick et al. 1980, Gold et al. 1978
Chinese hamster ovary/HGPRT assay	wk?	N.T.	wk§	Schenley et al. 1983
House lymphoma TK+/- assay	wk?	-	+	Litton Bionetics Inc., February 1978, Brusick et al. 1980
<u>Drosophila</u> sex-linked recessive lethal test	-	-	(+,-)§	Nix et al. 1983, Brusick et al. 1980, Valencia 1978
<b>Cytogenetic Tests:</b>				
<u>In vivo</u> rat bone marrow assay	rat	mice	mice	Litton Bionetics Inc., October 1978, Brusick et al. 1980, Furukawa et al. 1978, Nakanishi and Schneider 1979, Salamone and Katz 1981
	-	-	(wk?,-)§	
Sister chromatid exchange - <u>in vivo</u> mice	-	N.T.	+	Tice 1983, Nakanishi and Schneider 1979
<u>in vitro</u> mammalian cells	-	wk?	+	Tice 1983, Brusick et al. 1980, Furukawa et al. 1978
<b>Other Tests Indicative of DNA Damage Activity:</b>				
Rat hepatocyte primary culture/DNA repair test	-	-	+	Tong et al. 1983, U.S. EPA 1983
WI-38 unscheduled DNA synthesis	wk?	N.T.	N.T.	Litton Bionetics Inc., September 1978
Mitotic recombination in <u>Saccharomyces cerevisiae</u> D4	-?	-?	-?	Litton Bionetics Inc., June 1976, May 1978; Litton Bionetics Inc., August 1977

\*(-) designates negative, (+) positive response, (wk) weak response which was reproducible and dose-dependent, (wk?) marginal response which was not dose-dependent and/or not repeatable, (-?) questionable negative, and (N.T.) not tested.

†The authors listed did not necessarily evaluate all three chemicals listed.

§Repeatable but not dose-dependent.

#Nix et al. (1983) reported negative results, and Valencia (1978) reported positive results.

\*Nakanishi and Schneider (1979) and Salamone and Katz (1981) reported weak results and Furukawa et al. (1978) reported negative results.

Source: Mutagenicity Assessment of Fyrol PCF  
EPA Office of Health and Environmental Assessment  
November 1983. (OHEA-R-114)

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### Carcinogenicity of Fyrol PCF

No studies of carcinogenicity per se have been done with Fyrol PCF, at least none that I can find in the scientific literature. However, mutagenicity is a good predictor of carcinogenicity in that both require DNA damage (in the case of mutagenicity, damage to a gene within sperm or egg cells; in the case of carcinogenicity, damage to an oncogene of a somatic cell).

Many of the mutagenic tests of Fyrol PCF described above are valid "short-term tests" for predicting carcinogenicity, including the Ames test, unscheduled DNA synthesis induction and induction of sister chromatid exchanges. At least 90 percent of all known carcinogens, and perhaps 99 percent of all carcinogenic initiators, score positive in one or all of these tests. In that Fyrol PCF did not increase any of these effects over background, it can be stated with reasonable scientific certainty that Fyrol PCF will not be a carcinogenic initiator and with 90 percent assurance that it will also fail to be a promotor.

Hence, most likely, Fyrol PCF is not a carcinogen. Definitive proof of this fact must await animal testing, which, as far as I am aware, is not in progress at present.

### Toxicity of Fyrol PCF

Chronic genotoxic health problems such as mutagenicity and carcinogenicity are of main concern to EPA in assessing human risk from groundwater or surface water pollution. However, in this case of a finite spill, acute health effects are of equal importance, since the level of groundwater contamination at the Witco spill site in New Castle County, Delaware, should abate with time (although this abatement has not been demonstrated by available sampling).

In this regard, it is important to note that the acute toxicity of Fyrol PCF in the tests described above was surprisingly high. Acute toxicity of Fyrol PCF in many in vivo tests was 50 percent higher than for Tris BP and the former exposure levels had to be diluted accordingly. A review of the toxicity data leads me to calculate an upper limit of 1 ppm as the threshold value for human safety (assuming annual consumption of two liters of contaminated water per day).

### Conclusions

1. Fyrol PCF is not a mutagen.
2. Fyrol PCF is not a teratogen.
3. Fyrol PCF is probably not a carcinogen.
4. In some well samples at the New Castle County spill site Fyrol-PCF was found in excess of 100 ppm. Levels in excess of 1 ppm may pose acute toxicity to humans if consumed for one year or more.